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(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JUNGHEIM, Louis, Nickolaus** [US/US]; 8218 Meadowbrook Drive, Indianapolis, IN 46240 (US). **MCGILL, John, McNeill, III** [US/US]; 2254 Arden Place, Greenwood, IN 46143 (US). **THRASHER, Kenneth, Jeff** [US/US]; 8660 Count Turf Court, Indianapolis, IN 46217 (US). **HERR, Robert, Jason** [US/US]; 248 New Salem South, Voorheesville, NY 12186 (US). **MURALIKRISHNA, Valluri** [IN/US]; 11 Elm Court, Apartment C, Rensselaer, NY 12144 (US).

(74) Agents: **VOY, Gilbert, T.** et al.; ELI LILLY AND COMPANY, P.O. Box 6288, Indianapolis, IN 46206-6288 (US).

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(54) Title: COMPOUNDS, METHODS AND FORMULATIONS FOR THE ORAL DELIVERY OF A GLUCAGON LIKE PEPTIDE (GLP)-1 COMPOUND OR AN MELANOCORTIN 4 RECEPTOR (MC4) AGONIST PEPTIDE

(57) Abstract: The present invention relates to novel compounds, methods, and formulations useful for the oral delivery of a GLP-1 compound or an MC4 agonist peptide.

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(71) Applicant: **AMYLIN PHARMACEUTICALS, INC.**
San Diego
California 92121 (US)

(72) Inventors:
- **Young, Andrew**
  Point Loma, CA 92166 (US)
- **Gedulin, Bronislava**
  San Diego, CA 92131 (US)

(74) Representative: **Duckworth, Timothy John**
J.A. Kemp & Co.
14 South Square
Gray's Inn
GB-London WC1R 5JJ (GB)

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(54) Exendins for glucagon suppression

(57) Use of an exendin, an exendin agonist, a modified exendin or a modified exendin agonist in the manufacture of a pharmaceutical formulation for use in therapeutic lowering of plasma glucagon.

EP 1 658 856 A1

Description

BACKGROUND OF THE INVENTION

[0001] Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself. Biologically or chemically active agents are particularly vulnerable to such barriers. In the delivery to animals of biologically active or chemically active pharmacological and therapeutic agents, physical and chemical barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes that must be traversed before reaching a target, and examples of chemical barriers include, but are not limited to, variations in pH, lipid bilayers, and degrading enzymes.

[0002] These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as varying pH in the gastrointestinal (GI) tract, powerful digestive enzymes, and active agent impermeable gastrointestinal membranes. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents are rapidly rendered ineffective or are destroyed in the gastrointestinal tract by acid hydrolysis, enzymes, or the like.

[0003] Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of excipients or enhancers (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzyme inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate) to inhibit enzymatic degradation.

[0004] Liposomes have also been described as drug delivery systems for insulin and heparin. See, for example, U.S. Pat. No. 4,239,754; Patel et al (1976), FEBS Letters, Vol 62, pg. 60, and Hashimoto et al. (1970), Endocrinology Japan, Vol, 26, pg. 337.

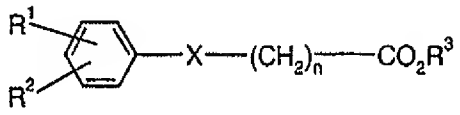
[0005] However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of excipients, enhancers or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) they exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

[0006] More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals. For example, U.S. Pat. No. 4,925,673 describes drug-containing proteinoid microsphere carriers as well as methods for their preparation and use. These proteinoid microspheres are useful for the delivery of a number of active agents.

[0007] Delivery agent molecules have also been disclosed in U.S. Patent Nos. 5,541,155; 5,693,338; 5,976,569; 5,643,957; 5,955,503; 6,100,298; 5,650,386; 5,866,536; 5,965,121; 5,989,539; 6,001,347; 6,071,510; 5,820,881; and 6,242,495; *see also* WO 02/02509; WO 01/51454; WO 01/44199; WO 01/32130; WO 00/59863; WO 00/50386; WO 00/47188; and WO 00/40203.

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention relates to a compound of formula I:

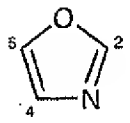


I;

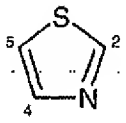
wherein

R^1 and R^2 are each independently H, OH, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, halo or $NR^4R^{4'}$;
R^3 is H, C_1-C_6 alkyl;
R^4 is H, COR^5, SO_2R^6, or C_1-C_6 alkyl;
$R^{4'}$ is H or C_1-C_6 alkyl;

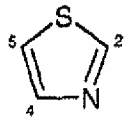
and the phenyl substituent is attached at carbon atom number 4 and the alkanoic acid chain is attached at carbon atom number 2;
X is



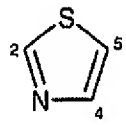
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;
X is



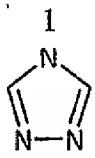
and the phenyl substituent is attached at carbon atom number 4 and the alkanoic acid is attached at carbon atom number 2;
X is



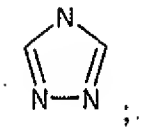
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;
X is



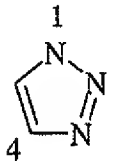
and the phenyl substituent is attached at carbon atom number 2 and the alkanoic acid is attached at carbon atom number 4;
X is



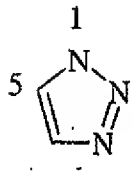
optionally substituted at nitrogen atom number 1 with methyl;
X is



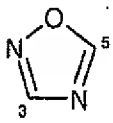
X is



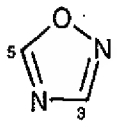
and the phenyl substituent is attached at carbon atom number 4 and the alkanoic acid is attached at nitrogen atom number 1;
X is



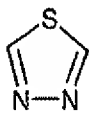
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at nitrogen atom number 1;
X is



and the phenyl substituent is attached at carbon atom number 3 and the alkanoic acid is attached at carbon atom number 5;
X is



and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 3;
X is



and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2.

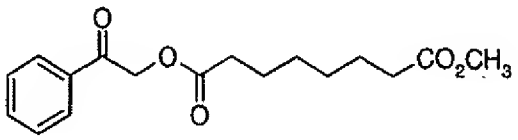
Preparations and Examples

[0023] All non-aqueous reactions are performed under a dry atmosphere of nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents are used as received from vendors and no attempts are made to purify or dry these components further. Removal of solvents under reduced pressure is accomplished with a Buchi rotary evaporator at approximately 28 mm Hg pressure using a Teflon-lined KNF vacuum pump. Thin layer chromatography is performed using 1" x 3" Analtech No. 02521, Whatman No. MK6F or EM Science (Merck) No. 5719-2 silica gel plates with fluorescent indicator. Visualization of TLC plates is made by observation with either short wave UV light, 10% phosphomolybdic acid in ethanol or in iodine vapors. Flash column chromatography is carried out using Kieselgel silica gel 60. Proton NMR spectra are obtained on a Bruker AC 300 MHz Nuclear Magnetic Resonance Spectrometer and are reported in ppm δ values, using tetramethylsilane as an internal reference. Melting points are obtained using an Electrothermal melting point apparatus and are uncorrected. CI Mass spectroscopic analyses are performed on a Shimadzu QP-5000 GC/Mass Spectrometer (methane) by direct injection. API Mass spectroscopic analyses are performed on a Finnegan LCQ Duo Ion Trap or a PESciex API 150EX mass spectrometer, using electro spray ionization (ESI) or atmospheric pressure chemical ionization (APCI). HPLC analyses are conducted using a Waters Symmetry C18, 5um, WAT046980, 3.9x150 mm column. The elution system consisted of 90:10 (0.1% TFA in H_2O)/(0.1% TFA in CH_3CN) gradient elution to 10:90 (0.1 % TFA in H_2O)/(0.1% TFA in CH_3CN) over 20 min, followed by 10:90 (0.1 % TFA in H_2O) /(0.1% TFA in CH_3CN) isocratic elution for 10 min, followed by 90:10 (0.1 % TFA in H_2O)/(0.1 % TFA in CH_3CN) isocratic elution for 10 min. The flow rate is 1 mL/min. UV Detection is performed at both 214 and 254 nm.

Preparation 1

Octanedioic Acid Methyl Ester 2-Oxo-2-phenylethyl Ester

[0024]

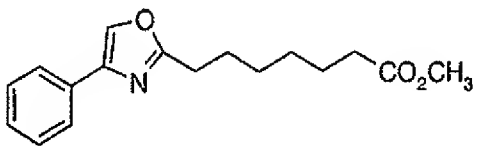


[0025] Add a solution of sodium bicarbonate (2.12 g, 25.2 mmol) in water (10 mL) to a solution of suberic acid monomethyl ester (4.75 g, 25.2 mmol) in methanol (50 mL) at room temperature and stir the mixture for 30 minutes. Remove the solvent under reduced pressure and add the residue to a solution of 2-bromoacetophenone (5.0 g, 25.1 mmol) in acetone (150 mL) at room temperature under nitrogen. Heat the mixture at reflux for 10 hours and then remove the solvent under reduced pressure. Dilute the residue with diethyl ether (300 mL), stir for 20 minutes, filter through a short silica gel column, and wash with diethyl ether (2 x 50 mL). Remove the solvent under reduced pressure to provide octanedioic acid methyl ester 2-oxo-2-phenylethyl ester (6.9 g, 90%).

Example 1

7-(4-Phenyloxazol-2-yl)heptanoic Acid Methyl Ester

[0026]



[0027] Heat a mixture of octanedioic acid methyl ester 2-oxo-2-phenylethyl ester (6.93 g; 22.6 mmol), acetamide (6.75 g, 114 mmol) and boron trifluoride diethyl etherate (3.0 mL, 23.7 mmol) at 135-140°C under nitrogen for 4 hours. Cool the mixture, dilute with saturated $NaHCO_3$ solution (100 mL), and extract with ethyl acetate (250 mL). Wash the organic

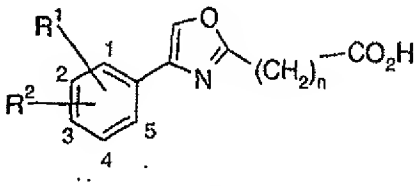
extract with 100 mL of saturated aqueous sodium chloride (brine) and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (85:15), to provide 7-(4-phenyloxazol-2-yl)heptanoic acid methyl ester (5.7 g, 88%).

Example 2

7-(4-Phenyloxazol-2-yl)heptanoic Acid

[0028] Add solution of sodium hydroxide (1.60 g, 40.0 mmol) in water (30 mL) to a solution of 7-(4-phenyloxazol-2-yl) heptanoic acid methyl ester (5.75 g, 20.0 mmol) in methanol (40 mL) at room temperature and heat the mixture at 40°C for 2 hours. Adjust the pH of the mixture to 2 with 1 N HCl and extract with ethyl acetate (600 mL). Wash the organic extract with water (3 x 150 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Triturate the residue with hexanes/ethyl acetate and collect the solids by filtration to provide 7-(4-phenyloxazol-2-yl)heptanoic acid (5.01 g, 91%): APCI mass spectrum *m/z* 272 $[C_{16}H_{19}NO_3 - H]^-$.

[0029] Prepare Examples 3-30, compounds of formula II(a) listed in Table 1 below, by the same process as in the preparation of Example 2.



II(a)

Table 1: Compounds of formula II(a)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
3	OCH_3 (1)	H	3	261 $[C_{14}H_{15}NO_4]^+$
4	OCH_3 (1)	H	4	276 $[C_{15}H_{17}NO_4 + H]^+$
5	OCH_3 (1)	H	5	290 $[C_{16}H_{19}NO_4 + H]^+$
6	OH (1)	H	4	260 $[C_{14}H_{15}NO_4 - H]^-$
7	OH (1)	OCH_3 (3)	4	290 $[C_{15}H_{17}NO_5 - H]^-$
8	OCH_3 (1)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
9	H	OCH_3 (3)	6	302 $[C_{17}H_{21}NO_4 - H]^-$
10	OH(1)	H	6	288 $[C_{16}H_{19}NO_4 - H]^-$
11	OH (1)	OCH_3(3)	6	318 $[C_{17}H_{21}NO_5 - H]^-$
12	OH (1)	Cl(4)	6	322 $[C_{16}H_{18}ClNO_4 - H]^-$
13	OH(1)	H	3	246 $[C_{13}H_{13}NO_4 - H]^-$
14	OH(1)	F (3)	4	280 $[C_{14}H_{14}FNO_4 + H]^+$
15	OH (1)	H	5	276 $[C_{15}H_{17}NO_4 + H]^+$
16	OCH_3(1)	H	2	248 $[C_{13}H_{13}NO_4+H]^+$
17	OH(1)	H	2	234 $[C_{12}H_{11}NO_4+ H]^+$
18	OH(1)	OCH_3(3)	3	276 $[C_{14}H_{15}NO_5 - H]^-$
19	H	H	4	246 $[C_{14}H_{15}NO_3 + H]^+$
20	F (1)	H	4	264 $[C_{14}H_{14}]FNO_3 + H]^+$
21	OCH_3(2)	H	4	276 $[C_{15}H_{17}NO_4 + H]^+$

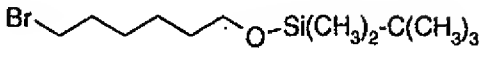
(continued)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
22	OH (2)	H	4	262 $[C_{14}H_{15}NO_4 + H]^+$
23	OH (1)	OH (3)	4	278 $[C_{14}H_{15}NO_5 + H]^+$
24	OH (1)	OCH_3 (3)	5	304 $[C_{13}H_{13}NO_4 - H]^-$
25	OH (1)	OH (5)	4	278 $[C_{14}H_{15}NO_5 + H]^+$
26	OH (1)	F (4)	4	278 $[C_{14}H_{14}FNO_4 - H]^-$
27	OH (1)	CN (4)	4	285 $[C_{15}H_{14}N_2O_4 - H]^-$
28	OH (1)	CN (3)	4	287 $[C_{15}H_{14}N_2O_4 + H]^+$
29	OH (1)	Br (3)	4	278 $[C_{14}H_{14}BrNO_4H]^+$
30	OH(1)	OCH_3(4)	4	290 $[C_{15}H_{17}FNO_5 - H]^-$
174	OH(1)	Cl(3)	4	294 $[C_{14}H_{14}ClNO_4 - H]^-$
175	OH(1)	Br (4)	4	339 $[C_{14}H_{14}BrNO_4 - H]^-$
176	OH (1)	CH_3(3)	4	276 $[C_{15}H_{17}N_2O_4 + H]^+$
177	OH (1)	CH_3(4)	4	276 $[C_{15}H_{17}N_2O_4 + H]^+$
178	OH(1)	$N(CH_3)_2$(3)	4	303 $[C_{16}H_{20}N_2O_4 - H]^-$
179	OH(1)	$NHSO_2CH_3$(4)	4	355 $[C_{15}H_{18}N_2O_6S + H]^+$.
180	OH(1)	$NHSO_2CH_3$(3)	4	355 $[C_{15}H_{18}N_2O_6S + H]^+$

Preparation 2

(6-Bromohexyloxy)-*tert*-butyldimethylsilane

[0030]

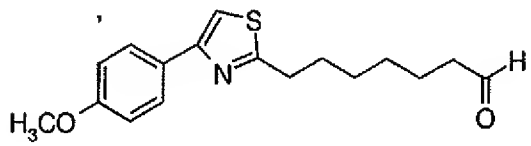


[0031] Add a solution of *tert*-butyldimethylsilyl chloride (5.0 g, 33.1 mmol) in dimethylforamide (DMF) (70 mL) dropwise over 15 minutes to a solution of 6-bromohexanol (5.0 g, 27.6 mmol) and imidazole (4.7 g, 69 mmol) in DMF (80 mL) at 0°C under nitrogen protection and stir the mixture for another 3.5 hours. Dilute the mixture with water (400 mL) and extract with diethyl ether (3 x 150 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with ethyl acetate/ hexanes (1:19), to provide (6-bromohexyloxy)-*tert*-butyldimethylsilane (8.05 g, 98%).

Preparation 3

7-[4-(4-Methoxyphenyl)thiazol-2-yl]heptanal

[0032]



[0033] Add a solution of thioacetamide (2.65 g, 34.9 mmol) in acetone (100 mL) dropwise to a solution of 2-bromo-4'-methoxyacetonephenone (8.0 g, 34.9 mmol) in acetone (100 mL) at room temperature under nitrogen. Stir the mixture for 12 hours. Collect the solids by filtration and wash with cold acetone (30 mL) to provide thioacetimidic acid 2-(4-methoxyphenyl)-2-oxoethyl ester hydrobromide (10.25 g, 96%).

[0034] Heat a mixture of thioacetimidic acid 2-(4-methoxyphenyl)-2-oxoethyl ester hydrobromide (10.0 g, 32.9 mmol) and zinc (II) chloride (4.50 g, 33.0 mmol) in methanol (80 mL) at reflux under nitrogen protection for 6.5 hours. Cool the mixture, slowly dilute with saturated $NaHCO_3$ (300 mL), and extract with methylene chloride (400 mL x 2). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (9:1), to provide 4-(4-methoxyphenyl)-2-methylthiazole (6.24 g, 92%): APCI mass spectrum *m/z* 206 $[C_{11}H_{11}NOS + H]^+$.

[0035] Add a solution of *tert*-butyllithium (26.35 mmol, 15.5 mL, 1.7 M in hexanes) dropwise to a solution of 4-(4-methoxyphenyl)-2-methylthiazole (6.15 g, 29.9 mmol) in degassed anhydrous tetrahydrofuran (THF) (100 mL) at -78°C under nitrogen and stir the solution for 45 minutes. To this solution, add a solution of (6-bromohexyloxy)-*tert*-butyldimethylsilane (7.20 g, 24.4 mmol) over 5 min and stir the mixture for 2 hours. Warm the mixture to 0°C, dilute with NH_4Cl (200 mL) and brine (250 mL) and extract with methylene chloride (3 x 150 mL). Dry the combined organic extracts over magnesium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (5:1), to provide 2-[7-(*tert*-butyldimethylsilanyloxy)heptyl]-4-(4-methoxyphenyl)thiazole (6.27 g, 50%).

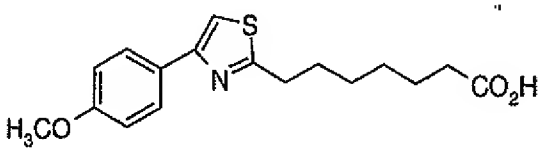
[0036] Add a solution of 1 N tetra-*n*-butylammonium fluoride (25.0 mmol, 25 mL, 1 M solution in THF) dropwise over 10 minutes to a solution of 2-[7-(*tert*-butyldimethylsilanyloxy)heptyl]-4-(4-methoxyphenyl)thiazole (6.27 g, 14.9 mmol) in anhydrous THF (50 mL) at 0°C under nitrogen and stir the mixture for 30 minutes at 0°C and then stir at room temperature for 3 hours. Dilute the mixture with brine (150 mL) and extract with ethyl acetate (100 mL x 3). Dry the combined organic extracts over magnesium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:2), to give 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptan-1-ol (4.07 g, 89%): APCI mass spectrum *m/z* 306 $[C_{17}H_{23}NO_2S + H]^+$.

[0037] Add anhydrous dimethyl sulfoxide (0.25 mL, 3.52 mmol) dropwise over 2 minutes to a solution of oxalyl chloride (393 mg, 3.10 mmol) in methylene chloride (10 mL) at -78°C under nitrogen and stir the mixture for 20 minutes. Add a solution of 7-[4-(4-methoxyphenyl) thiazol-2-yl]heptan-1-ol (0.609 g, 1.99 mmol) in methylene chloride (10 mL) dropwise in 5 minutes and then stir the mixture for 30 minutes. To this mixture, add triethylamine (1.0 mL, 7.2 mmol), stir and warm the reaction mixture to room temperature for 40 minutes. Dilute the mixture with ethyl acetate (100 mL), wash with brine (3 x 30 mL), dry over sodium sulfate and remove the solvent under reduced pressure to provide 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptanal (0.6 g, 99%): APCI mass spectrum *m/z* 304 $[C_{17}H_{21}NO_2S + H]^+$.

Example 31

7-[4-(4-Methoxyphenyl)thiazol-2-yl]heptanoic Acid

[0038]



[0039] Add 2-methyl-2-butene (7.0 mL) and sodium hypochlorite (2.51 g, 27.75 mmol) to a solution of 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptanal (4.02 g, 13.25 mmol) and potassium dihydrogen phosphate (3.10 g, 22.78 mmol) in *tert*-butanol (60 mL) and water (12 mL) at room temperature. Stir the mixture for 40 minutes, dilute with ethyl acetate (500 mL) and wash with brine (3 x 200 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:19), and triturate the residue with hexanes/methylene chloride to afford 7-[4-(4-methoxyphenyl) thiazol-2-yl]heptanoic acid (3.91 g, 88%): APCI MS *m/z* 320 $[C_{17}H_{21}NO_3S + H]^+$.

[0040] Prepare Examples 32 and 33, compounds of formula II(b) listed in Table 2 below, by the same process as in the preparation of Example 31.

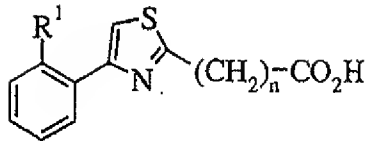


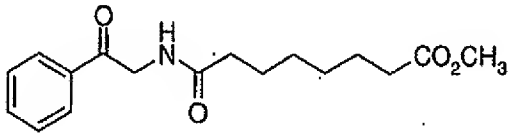
Table 2: Compounds of formula II(b)

Example	R^1	n	mass spectrum *m/z*
32	OCH_3	6	318 $[C_{17}H_{21}NO_3S - H]^-$
33	OH	6	304 $[C_{16}H_{19}NO_3S - H]^-$
181	OH	4	276 $[C_{14}H_{15}NO_3S - H]^-$

Preparation 4

7-(2-Oxo-2-phenylethylcarbamoyl)heptanoic Acid Methyl Ester

[0041]



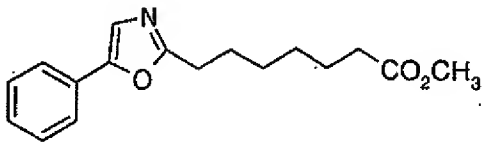
[0042] Add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide(EDC) (8.5 g, 44.3 mL) to a solution of 2-amino-1-phenylethanol (5.0 g, 36.4 mmol), suberic acid monomethyl ester (6.85 g, 36.4 mmol) and 1-hydroxybenzotriazole (HOBt, 5.0 g, 37.0 mmol) in THF (200 mL) at room temperature under nitrogen. Stir the mixture for 12 hours. Dilute the mixture with ethyl acetate (600 mL), wash with 1N HCl (2 x 150 mL), brine (2 x 150 mL), $NaHCO_3$ (2 x 150 mL) and brine (150 mL) solutions and dry over sodium sulfate. Remove the solvent under reduced pressure to provide 7-(2-hydroxy-2-phenylethylcarbamoyl)heptanoic acid methyl ester (10.3 g, 91 %), which is used in the following step without purification.

[0043] Add Dess-Martin periodinane (16.5 g, 38.7 mmol) to a solution of 7-(2-hydroxy-2-phenylethylcarbamoyl)heptanoic acid methyl ester (10.2 g, 33.3 mmol) in methylene chloride (360 mL) at 0°C under nitrogen, stir and warm the mixture to room temperature for 4 hours. Filter the mixture through Celite, wash with ethyl acetate (3 x 100 mL) and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (60:40), to provide 7-(2-oxo-2-phenylethylcarbamoyl)heptanoic acid methyl ester (7.33 g, 72%).

Example 34

7-(5-Phenyloxazol-2-yl)heptanoic Acid Methyl Ester

[0044]



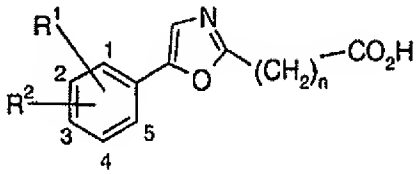
[0045] Add a solution of 7-(2-oxo-2-phenylethylcarbamoyl)heptanoic acid methyl ester (7.05 g, 23.1 mmol) and carbon tetrabromide (11.3 g, 34.3 mmol) in methylene chloride over 40 minutes to a mixture of triphenylphosphine (9.0 g, 34.3 mmol) and DMAP (5.51 g, 45.1 mmol) in methylene chloride (500 mL) at room temperature under nitrogen. Stir the mixture for 30 minutes and add additional triphenylphosphine (2.6 g, 9.92 mmol) and carbon tetrabromide (3.35 g, 10.1 mmol). Stir the mixture for an additional 20 minutes, filter through Celite and wash with ethyl acetate (3 x 100 mL). Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (70:30), to provide 7-(5-phenyloxazol-2-yl)heptanoic acid methyl ester (2.75 g, 41%).

Example 35

7-(5-Phenyloxazol-2-yl)heptanoic Acid

[0046] Add a solution of sodium hydroxide (1.80 g, 45.0 mmol) in water (30 mL) to a solution of 7-(5-phenyloxazol-2-yl)heptanoic acid methyl ester (9.0 g, 31.3 mmol) in methanol (30 mL) at room temperature and stir the mixture for 4 hours. Adjust the pH of the mixture to 2 with 1 N HCl and extract with ethyl acetate (500 mL). Wash the combined organic layers with water (3 x 100 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Crystallize the residue from ethyl acetate/hexanes to afford 7-(5-phenyloxazol-2-yl)heptanoic acid (7.3 g, 85%): APCI mass spectrum *m/z* 272 $[C_{16}H_{19}NO_3 - H]^-$.

[0047] Prepare Examples 36-41, compounds of formula II(c) listed in Table 3 below, by the same process as in the preparation of Example 35.



II(c)

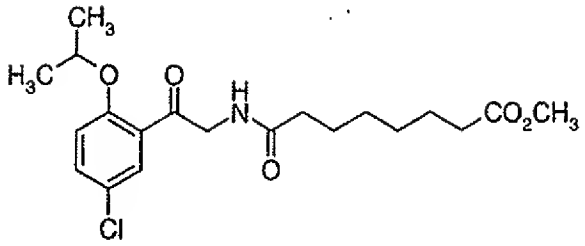
Table 3: Compounds of formula II(c)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
36	OCH_3 (3)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
37	OH (1)	Cl (4)	6	321 $[C_{16}H_{18}ClNO_4 - H]^-$
38	OCH_3 (1)	OCH_3 (4)	6	332$[C_{18}H_{23}NO_5 - H]^-$
39	OH (1)	H	4	260 $[C_{14}H_{15}NO_4 - H]^-$
40	OCH_3 (1)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
41	OH (1)	H	6	288 $[C_{16}H_{19}NO_4 - H]^-$

Preparation 5

7-[2-(5-Chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]heptanoic Acid Methyl Ester

[0048]



[0049] Add 2-iodopropane (63.3 mL, 633 mmol) dropwise to a suspension of 1-(5-chloro-2-hydroxyphenyl)ethanone (90.0 g, 528 mmol) and potassium carbonate (109.46 g, 792mmol) in DMF (1000 mL) at room temperature under nitrogen and heat the mixture at 80°C for 22 hours. Cool and filter the mixture and remove the solvent reduced pressure. Dilute the residue with ethyl acetate (1 L), wash with water (300 mL) and brine (200 mL), dry over sodium sulfate, and remove the solvent under reduced pressure to afford 1-(5-chloro-2-isopropoxyphenyl)ethanone (104.78 g, 93%).

[0050] Add Copper(II) bromide (199 g, 891 mmol) portionwise to a solution of 1-(5-chloro-2-isopropoxyphenyl)ethanone (94.74 g, 446 mmol) in ethyl acetate (500 mL) and chloroform (500 mL) at room temperature under nitrogen. Heat the mixture at reflux for 4.5 hours. Cool the mixture and vacuum filter through a plug of Celite, washing with ethyl acetate (1 L). Remove the solvents under reduced pressure to provide 2-bromo-1-(5-chloro-2-isopropoxyphenyl)ethanone (128.46 g, 98%).

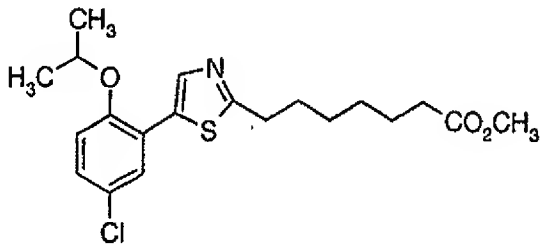
[0051] Add hexamethylenetetramine (36.14 g, 258 mmol) to a solution of 2-bromo-1-(5-chloro-2-isopropoxyphenyl) ethanone (75.17 g, 258 mmol) in chloroform (400 mL) at room temperature under nitrogen and stir for 2 days. Collect the solids by filtration, wash with diethyl ether, and dry overnight under reduced pressure. Suspend the solids in methanol (350 ml), cool to 0°C, and treat slowly with concentrated HCl (113 ml, 1365 mmol). Warm the mixture to room temperature and stir for 40 hours. Then heat the mixture to 55°C for an additional 4 hours. Remove the solids by filtration, and remove the filtrate solvent under reduced pressure to provide a solid. Triturate the solid with diethyl ether. Collect the resulting material by filtration to provide 2-amino-1-(5-chloro-2-isopropoxyphenyl)ethanone hydrochloride, which is used in the next step without purification.

[0052] Add diisopropylethylamine (99 ml, 568 mmol) dropwise to a solution of EDC HCl (38.01 g, 198 mmol), HOBt (19.19 g, 142 mmol) and octanedioic acid monomethyl ester (53.44 g, 1.42 mmol) in methylene chloride (800 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for 1 hour. Add 2-amino-1-(5-chloro-2-isopropoxyphenyl)ethanone hydrochloride (53.44 g, 142 mmol) to the mixture and stir for 18 hours. Remove the solvent under reduced pressure, dilute the residue in ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), and dry over magnesium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (4:6 to 0:10), to afford 7-[2-(5-chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]-heptanoic acid methyl ester (23.87 g, 23% over three steps).

Example 42

7-[5-(5-Chloro-2-isopropoxyphenyl)thiazol-2-yl]heptanoic Acid Methyl Ester

[0053]



[0054] Add Lawesson's reagent (31.03 g, 77 mmol) to a solution of 7-[2-(5-chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]heptanoic acid methyl ester (21.80 g, 55 mmol) in THF (550 mL) at room temperature under nitrogen. Heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:3), to afford 7-[5-(5-chloro-2-isopropoxyphenyl)

thiazol-2-yl]heptanoic acid methyl ester (9.96 g, 46%).

Example 43

7-[5-(5-Chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic Acid Methyl Ester

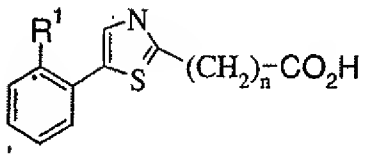
[0055] Add aluminum(III) chloride (6.67 g, 50 mmol) portionwise to a solution of 7-[5-(5-chloro-2-isopropoxyphenyl) thiazol-2-yl]heptanoic acid methyl ester (9.90 g, 25 mmol) in methylene chloride (300 mL) at 0°C under nitrogen. Slowly warm the mixture to room temperature and stir for an additional 30 minutes. Cool the mixture to 0°C, treat with saturated aqueous sodium sulfate Na_2SO_4 (150 ml), and stir for 1 hour. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9 to 1:1), to afford 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (5.67 g, 64%).

Example 44

7-[5-(5-Chloro-2-hydroxy-phenyl)-thiazol-2-yl]-heptanoic acid

[0056] Add a solution of sodium hydroxide (2.60 g, 65 mmol) in water (50 mL) to a solution of 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (5.76 g, 16 mmol) in methanol (100 mL) at 0°C under nitrogen., warm the mixture to room temperature, and stir for a total of 1.5 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the precipitate by filtration to afford 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid (5.21g, 95%): APCI mass spectrum *m/z* 338 $[C_{16}H_{18}ClNO_3S - H]^-$.

[0057] Prepare Examples 45-47, compounds of formula II(d) listed in Table 4 below, by the same process as in the preparation of Example 44.



II(d)

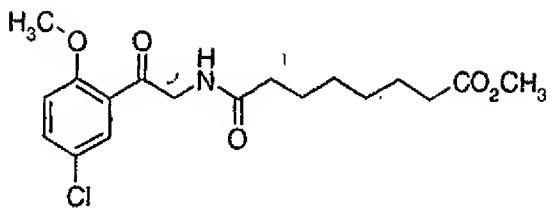
Table 4: Compounds of formula II(d)

Example	R^1	n	mass spectrum *m/z*
45	OCH_3	6	320 $[C_{17}H_{21}NO_3S + H]^+$
46	OH	6	304 $[C_{16}H_{19}NO_3S - H]^-$
47	OH	4	276 $[C_{14}H_{15}NO_3S - H]^-$

Preparation 6

7-[2-(2-Methoxyphenyl)-2-oxoethylcarbamoyl]heptanoic Acid Methyl Ester

[0058]

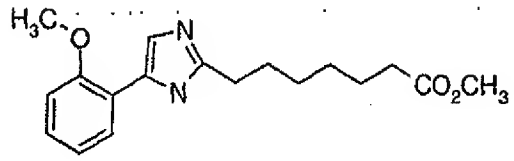


[0059] Add triethylamine (8.1 g, 79.9 mmol) dropwise to a solution of 2-amino-1-(2-methoxyphenyl)ethanone hydrochloride (13.6 g, 67.4 mmol) and octanedioic acid monomethyl ester (14.0 g, 74.2 mmol) in methylene chloride (600 mL) at 0°C under nitrogen, and then add EDC HCl (15.5 g, 81.0 mmol). Stir the mixture for 4 hours and warm to room temperature with stirring for an additional 18 hours. Dilute the mixture in ethyl acetate (1.2 L), wash sequentially with water (300 mL), 1 N HCl (300 mL), brine (300 mL), saturated sodium, bicarbonate solution (300 mL) and brine (300 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure to afford 7-[2-(2-methoxyphenyl)-2-oxoethylcarbamoyl]heptanoic acid methyl ester (20.0 g, 88%), which is used in the next step without further purification.

Example 48

7-[5-(2-Methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic Acid Methyl Ester

[0060]



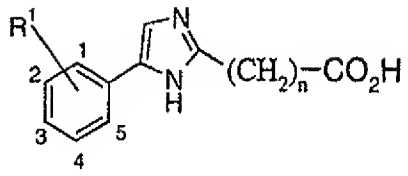
[0061] Heat a mixture of ammonium acetate (16.5 g, 214 mmol) and 7-[2-(2-methoxyphenyl)-2-oxoethylcarbamoyl] heptanoic acid methyl ester (14.2 g, 42.3 mmol) in acetic acid (300 mL) at reflux under nitrogen for 15 hours. Remove the solvent under reduced pressure. Dilute the residue in ethyl acetate (500 mL) and adjust to pH 8 with saturated aqueous sodium bicarbonate solution. Extract the aqueous layer with additional ethyl acetate (200 mL) and dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate, to afford 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid methyl ester (5.86 g, 44%): APCI mass spectrum *m/z* 317 $[C_{18}H_{24}N_2O_3 + H]^+$.

Example 49

7-[5-(2-Methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic Acid

[0062] Add a solution of sodium hydroxide (1.85 g, 46 mmol) in water (40 mL) to a solution of 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid methyl ester (5.84 g, 18.5 mmol) in methanol (30 mL) at room temperature under nitrogen and heat the mixture at 40°C for 4.5 hours. Cool the mixture and treat with 1 N HCl (46 mL) and heat at reflux for 30 minutes. Collect the precipitate, wash with water (3 x 30 mL), and dry under reduced pressure for 12 hours. Triturate the solid with methylene chloride (50 mL) at reflux for 40 min and collect by filtration to provide 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid (4.27 g, 77%). APCI mass spectrum *m/z* 301 $[C_{17}H_{22}N_2O_3 - H]^-$.

[0063] Prepare Examples 50-55, compounds of formula II(e) listed in Table 5 below, by the same process as in the preparation of Example 49.



II(e)

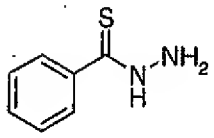
Table 5: Compounds of formula II(e)

Example	R^1(position on ring)	n	mass spectrum *m/z*
50	H	6	271[$C_{16}H_{20}N_2O_2$-H]$^-$
51	OCH_3(3)	6	301[$C_{17}H_{22}N_2O_3$-H]$^-$
52	OH (3)	6	287[$C_{16}H_{20}N_2O_3$-H]$^-$
53	OH (1)	6	287[$C_{16}H_{20}N_2O_3$-H]$^-$
54	OCH_3 (1)	4	273[$C_{15}H_{18}N_2O_3$-H]$^-$
55	OH (1)	4	282[$C_{14}H_{15}N_2NaO_3$]$^-$

Preparation 7

Thiobenzoic Acid Hydrazide

[0064]



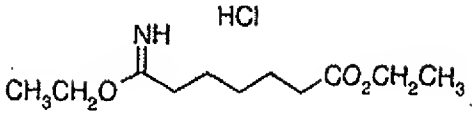
[0065] Add a solution of thiobenzoylsulfanylacetic acid (5.5 g, 26.0 mmol) in methanol (100 mL) and to a solution of thionyl chloride (52 mL) at room temperature under nitrogen and heat the mixture at reflux for 12 hours. Remove the solvent under reduced pressure, dissolve the residue in ethyl acetate (200 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions, and dry over sodium sulfate. Remove the solvent under reduced pressure to provide thiobenzoylsulfanylacetic acid methyl ester (5.7 g, 97%).

[0066] Add a solution of thiobenzoylsulfanylacetic acid methyl ester (1.9 g, 8.4 mmol) in ethanol (30 mL) to a solution of anhydrous hydrazine(1 mL) at room temperature under nitrogen and stir for 2 hours. Then add water (20 mL) and remove the solvent under reduced pressure. Dissolve the residue in ethyl acetate (300 mL), wash with water (200 mL) and brine (200 mL), and dry over magnesium sulfate. Remove the solvent under reduced pressure to provide thiobenzoic acid hydrazide (1.2 g, 94%).

Preparation 8

7-Ethoxycarbonimidoylheptanoic Acid Ethyl Ester Hydrochloride

[0067]



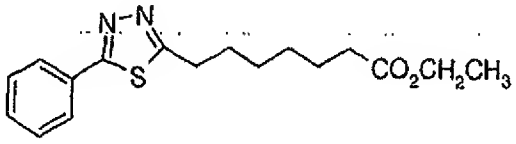
[0068] Add sodium cyanide (12.5 g, 255 mmol) and tetra-*n*-butylammonium iodide (10 g, 27.0 mmol) portionwise to a solution of 7-bromoheptanoic acid methyl ester (25 g, 105 mmol) in DMSO (300 mL) at room temperature under nitrogen and heat the mixture at 50°C for 4 hours. Cool the mixture and dilute with water (200 mL) and extract with diethyl ether (2 x 200 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure to provide 7-cyanoheptanoic acid ethyl ester (18.2 g, 94%).

[0069] Bubble hydrogen chloride gas into a solution of 7-cyanoheptanoic acid ethyl ester (3.7 g, 20.0 mmol) in ethanol (24 mL, 40 mmol) and diethyl ether (100 mL) at 0°C for 15 minutes. Remove the solvent under reduced pressure to provide 7-ethoxycarbonimidoylheptanoic acid ethyl ester (5.4 g, >99%), which is used without further purification.

Example 56

7-(5-Phenyl[1,3,4]thiadiazol)heptanoic Acid Ethyl Ester

[0070]



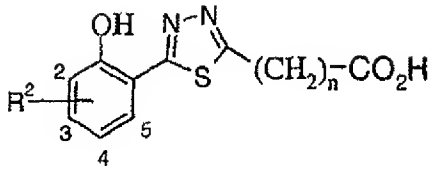
[0071] Heat a solution of thiobenzoic hydrazide (1.2 g, 7.90 mmol) and 7-ethoxycarbonimidoylheptanoic acid ethyl ester (2.9g, 11.0 mmol) in ethanol (35 mL) at reflux under nitrogen for 3 hours. Remove the solvent under reduced pressure. Dissolve the residue in ethyl acetate (200 mL), wash with water (200 mL) and brine (200 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (4:1), to provide 7-(5-phenyl[1,3,4]thiadiazol)heptanoic acid ethyl ester (1.15 g, 45%).

Example 57

7-(5-Phenyl[1,3,4]thiadiazol-2-yl)heptanoic Acid

[0072] Add a solution of potassium hydroxide (1.2 g 23 mmol) in water (50 mL) to a solution of 7-(5-phenyl-[1,3,4] thiadiazol)heptanoic acid ethyl ester (3.4 g, 11 mmol) in THF (30 mL) and methanol (30 mL) at room temperature under nitrogen and heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with ethyl acetate (200 mL). Adjust the pH of the aqueous layer to 3 with concentrated HCl and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate and remove the solvent under reduced pressure to afford 7-(5-phenyl[1,3,4]thiadiazol-2-yl)heptanoic acid (2.9 g, 93%). APCI mass spectrum *m/z* 289 $[C_{15}H_{18}N_2O_2S - H]^-$.

[0073] Prepare Examples 58-61, compounds of formula II(f) listed in Table 6 below, by the same process as in the preparation of Example 57.



II(f)

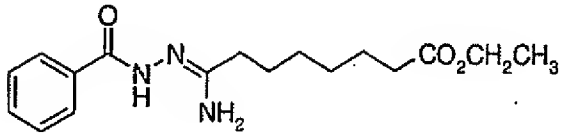
Table 6: Compounds of formula II(f)

Example	R^2(position on ring)	n	mass spectrum *m/z*
58	OCH_3 (3)	6	335 $[C_{16}H_{20}N_2O_4S - H]^-$
59	H	6	305 $[C_{15}H_{18}N_2O_3S - H]^-$
60	Cl (4)	6	341 $[C_{15}H_{17}ClN_2O_3S + H]^+$
61	H	4	277 $[C_{13}H_{14}N_2O_3S - H]^-$

Preparation 9

8-Amino-8-(benzoylhydrazono)octanoic Acid Ethyl Ester

[0074]

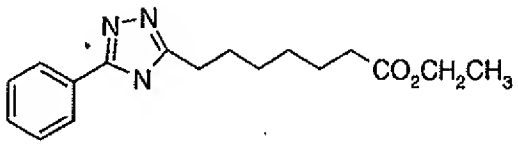


[0075] Add triethylamine (5.6 mL, 40 mmol) to a solution of 7-ethoxycarbonimidoylheptanoic acid ethyl ester (11.0 g, 41 mmol) and benzoic acid hydrazide (5.5 g, 40 mmol) in ethanol (110 mL) at room temperature under nitrogen and stir the mixture for 12 hours. Remove the solvent under reduced pressure, dissolve the residue in ethyl acetate (200 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions, and dry over sodium sulfate. Remove the solvent under reduced pressure to provide 8-amino-8-(benzoylhydrazono)octanoic acid ethyl ester (8.3 g, 64%).

Example 62

7-(5-Phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic Acid Ethyl Ester

[0076]



[0077] Heat a solution of 8-amino-8-(benzoylhydrazono)octanoic acid ethyl ester (4.2 g, 26 mmol) in o-xylene (400 mL) at reflux under nitrogen for 5 hours and then remove the solvent under reduced pressure. Dilute the residue with ethyl acetate (500 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions and dry over sodium sulfate.

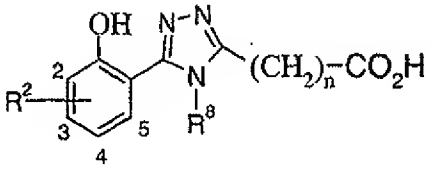
Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:9), to provide 7-(5-phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic acid ethyl ester (2.2 g, 58%).

Example 63

7-(5-Phenyl-4*H*-[1,3,4]triazol-3-yl)-heptanoic acid

[0078] Add a solution of potassium hydroxide (1.8 g, 32 mmol) in water (70 mL) to a solution of 7-(5-phenyl-4*H*-[1,3,4] triazol-3-yl)heptanoic acid ethyl ester (4.9 g, 16 mmol) in THF (50 mL) and methanol (50 mL) at room temperature under nitrogen and heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with ethyl acetate (200 mL). Adjust the pH of the aqueous layer to 3 with concentrated HCl and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate and remove the solvent under reduced pressure to afford 7-(5-phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic acid (4.4 g, 99%). APCI mass spectrum *m/z* 273 $[C_{15}H_{19}N_3O_2]^-$.

[0079] Prepare Examples 64-39, compounds of formula II(g) listed in Table 7 below, by the same process as in the preparation of Example 63.



II(g)

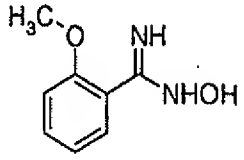
Table 7: Compounds of formula II(g)

Example	R^2(position on ring)	R^8	n	mass spectrum *m/z*
64	OCH_3(3)	H	6	319$[C_{16}H_{21}N_3O_4 - H]^-$
65	H	H	6	289$[C_{15}H_{19}N_3O_3-H]^-$
66	Cl(4)	H	6	323$[C_{15}H_{18}ClN_3O_3 - H]^-$
67	H	H	4	261 $[C_{13}H_{15}N_3O_3]^-$
68	H	CH_3	4	277$[C_{14}H_{17}N_3O_3]^-$

Preparation 10

N-Hydroxy-2-methoxybenzamidine

[0080]



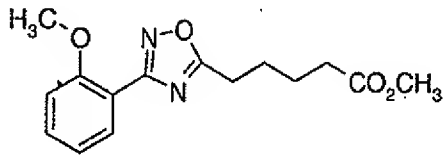
[0081] Add potassium hydroxide (30.3 g, 225 mmol) to a solution of 2-methoxybenzonitrile (25.0 g, 187 mmol) and hydroxylamine hydrochloride (15.77 g, 225 mmol) in ethanol (500 mL) at room temperature under nitrogen and heat the mixture at reflux for 12 hours. Remove the solvent under reduced pressure, triturate the residue with ethyl acetate/

hexanes (1:9, 300 mL) and collect by vacuum filtration to provide *N*-hydroxy-2-methoxybenzamidine (24.0 g, 91%).

Example 69

5-[3-(2-Methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic Acid Methyl Ester

[0082]



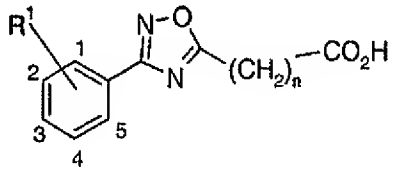
[0083] Add 5-chlorocarbonylpentanoic acid methyl ester (15.30 g, 86 mmol) to a solution of *N*-hydroxy-2-methoxybenzamidine (12.0 g, 71 mmol) in pyridine (40 mL) and under nitrogen at a rate to keep the mixture at a gentle reflux. Then, heat the mixture at reflux for 4 hours. Dilute the mixture with water (300 mL) and extract with methylene chloride (3 x 200 mL). Wash the combined organic extracts with brine (100 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:19), to afford 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid methyl ester (12.8 g, 55%).

Example 70

5-[3-(2-Methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic Acid

[0084] Add 2 N sodium hydroxide (20 mL) to a solution of 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid methyl ester (4.00 g, 13 mmol) in methanol (100 mL) at room temperature under nitrogen and stir the mixture for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with diethyl ether (200 mL). Adjust the aqueous layer to pH 1 with 2 N HCl and collect the solids by vacuum filtration to afford 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid (3.65 g, 99%). APCI mass spectrum *m/z* 275 $[C_{14}H_{16}N_2O_4 - H]^-$.

[0085] Prepare Examples 71-73, compounds of formula II(h) listed in Table 8 below, by the same process as in the preparation of Example 40.



II(h)

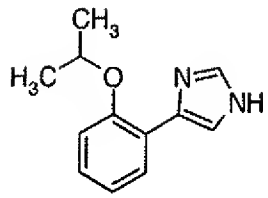
Table 8: Compounds of formula II(h)

Example	R^1(position on ring)	N	mass spectrum *m/z*
71	OH(1)	4	261 $[C_{13}H_{14}N_2O_4 - H]^-$
72	CH_3 (2)	7	301 $[C_{17}H_{22}N_2O_3 - H]^-$
73	CF_3(3)	7	355 $[C_{17}H_{19}F_3N_2O_3 - H]^-$

Preparation 11

4-(2-Isopropoxy-phenyl)-1*H*-imidazole

[0086]

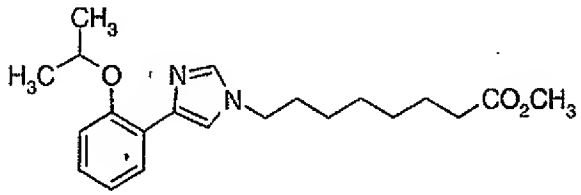


[0087] Add tetrakis(triphenylphosphine)palladium(0) (500 mg) to a degassed suspension of 4-bromo-1*H*-imidazole (5.0 g, 34 mmol) and 2-isopropoxyphenyl boronic acid (9.19 g, 51 mmol) in dioxane (250 mL) and 2 M sodium carbonate solution (10.81 g, 102 mmol) at room temperature under nitrogen and heat the mixture at reflux for 21 hours. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (500 mL) and filter through a plug of Celite. Dry the filtrate over sodium sulfate, treat with silica gel (20 g) and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate, to afford crude 4-(2-isopropoxyphenyl)-1*H*-imidazole (5.01 g, 73%) which is used without further purification in the next step.

Example 74

8-[4-(2-Isopropoxyphenyl)imidazol-1-yl]octanoic Acid Methyl Ester

[0088]



[0089] Add sodium hydride (1.82 g, 38 mmol) to a suspension of 4-(2-isopropoxyphenyl)-1*H*-imidazole (5.01 g, 25 mmol) in THF (125 mL) at 0°C under nitrogen, and warm the mixture to room temperature and stir for 1 hour. Cool the mixture to 0°C and add 8-bromooctanoic acid methyl ester (5.98 g, 25 mmol) and tetra-*n*-butylammonium iodide (0.55 g, 1.5 mmol) and warm the mixture to room temperature to stir for 8 hours. Dilute the mixture with water (20 mL) and remove the solvent under reduced pressure. Dilute the residue with ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), dry over sodium sulfate, and remove the solvent under reduced pressure to provide 8-[4-(2-isopropoxyphenyl)imidazol-1-yl]octanoic acid methyl ester (5.16 g, 57%), which is used in the next step without further purification.

Example 75

8-[4-(2-Hydroxyphenyl)imidazol-1-yl]octanoic Acid Methyl Ester

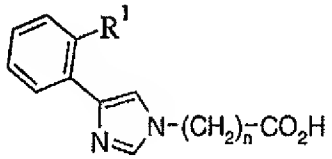
[0090] Add aluminum(III) chloride (3.84 g, 29 mmol) to a suspension of 8-[4-(2-isopropoxyphenyl)imidazol-1-yl]octanoic acid methyl ester (5.16 g, 14 mmol) in methylene chloride (150 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for 6 hours. Dilute the mixture with saturated aqueous sodium sulfate (50 mL) and remove the solvent under reduced pressure: Dilute the residue with ethyl acetate (300 mL), wash with brine (100 mL), dry over sodium sulfate, and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (2:8 to 3:7), to provide 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid methyl ester (2.63 g, 57%).

Example 76

8-[4-(2-Hydroxyphenyl)imidazol-1-yl]octanoic Acid

[0091] Add sodium hydroxide (1.32 g, 33 mmol) in water (20 mL) to a suspension of 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid methyl ester (2.60 g, 8 mmol) in methanol (50 mL) at 0°C under nitrogen and warm the mixture to room temperature and stir for 8 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the precipitate to provide 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid (1.70 g, 68%). APCI mass spectrum *m/z* 301 $[C_{17}H_{22}N_2O_3 - H]^-$.

[0092] Prepare Examples 77 and 78, compounds of formula II(i) listed in Table 9 below, by the same process as in the preparation of Example 76.



II(i)

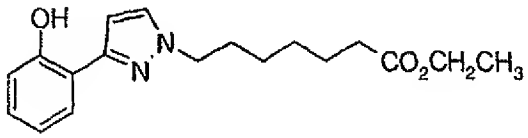
Table 9: Compounds of formula II(i)

Example	R^1	n	mass spectrum *m/z*
77	H	7	285$[C_{17}H_{22}N_2O_2 - H]^-$
78	OH	4	259 $[C_{14}H_{16}N_2O_3 - H]^-$

Example 79

7-[3-(2-Hydroxyphenyl)pyrazol-1-yl]heptanoic Acid Ethyl Ester

[0093]



[0094] Add sodium hydride (1.50 g, 31 mmol, 60% suspension in mineral oil) to a suspension of 2-(1*H*-pyrazol-3-yl) phenol (5.0 g, 31 mmol) and 7-bromoheptanoic acid ethyl ester (7.4 g, 31 mmol) in DMF (75 mL) at room temperature under nitrogen and heat the mixture at 75°C for 16 hours. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (300 mL), wash with water (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (9:1), to provide 7-[3-(2-hydroxyphenyl)pyrazol-1-yl]heptanoic acid ethyl ester (4.73 g, 48%).

Example 80

7-[3-(2-Methoxyphenyl)pyrazol-1-yl]heptanoic Acid Ethyl Ester

[0095] Add sodium hydride (900 mg, 18 mmol, 60% suspension in mineral oil) to a suspension of 7-[3-(2-hydroxyphenyl) pyrazol-1-yl]heptanoic acid ethyl ester (4.73 g, 15 mmol) and iodomethane (1.1 mL, 18 mmol) in THF (70 mL) at 0°C under nitrogen and warm the mixture to room temperature to stir for 12 hours. Remove the solvent under reduced

under reduced pressure, dissolve the residue in chloroform (200 mL), wash with water (100 mL) and brine (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:9), to afford 8-(2-phenylimidazol-1-yl)octanoic acid methyl ester (4.90 g, 47%).

Example 89

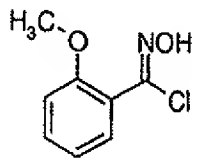
8-(2-Phenylimidazol-1-yl)octanoic Acid

[0100] Add sodium hydroxide (6.0 g, 150 mmol) in water (50 mL) to a suspension of 8-(2-phenylimidazol-1-yl)octanoic acid methyl ester (7.60 g, 25 mmol) in methanol (100 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for a total of 8 hours. Remove the solvent under reduced pressure, dilute the residue with water (300 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the precipitate and triturate with hexanes to afford 8-(2-phenylimidazol-1-yl)octanoic acid (4.22 g, 52%). APCI mass spectrum *m/z* 285 $[C_{17}H_{22}N_2O_2 - H]^-$.

Preparation 12

2-Methoxy-*N*-hydroxybenzenecarboxyimidoyl Chloride

[0101]



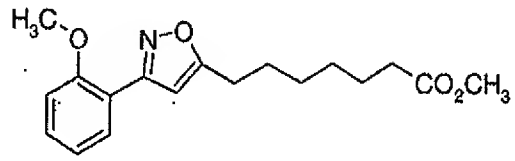
[0102] Add sodium hydroxide (8.50 g, 220 mmol) in water (150 mL) to a solution of o-anisaldehyde (25.0 g, 180 mmol) and hydroxylamine hydrochloride (15.4 g, 220 mmol) in ethanol (150 mL) and water (150 mL) at room temperature and stir the mixture for 3 hours. Acidify the mixture to pH 6 with 1 N HCl solution and collect the solids by vacuum filtration to provide 2-methoxybenzaldehyde oxime (32.0 g, 99%).

[0103] Add *N*-Chlorosuccinimide (8.30 g, 65 mmol) portionwise to a solution of 2-methoxybenzaldehyde oxime (10.0 g, 65 mmol) in DMF (100 mL) at room temperature under nitrogen. Heat the mixture at 50°C for 5 hours. Pour the mixture into ice water (300 mL) collect the solids by vacuum filtration to provide 2-methoxy-*N*-hydroxybenzenecarboxyimidoyl chloride (9.80 g, 81%).

Example 90

7-[3-(2-Methoxyphenyl)isoxazol-5-yl]heptanoic Acid Methyl Ester

[0104]



[0105] Add triethylamine (8.08 g, 80 mmol) to a solution of 2-methoxy-*N*-hydroxybenzenecarboxyimidoyl chloride (8.0 g, 40 mmol) and methyl 7-oxtynoate (10.50 g, 50 mmol) in THF (100 mL) at room temperature and stir the mixture for 24 hours. Dilute the mixture with water (500 mL) and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with water (100 mL) and brine (100 mL) and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to afford 7-[3-(2-methoxyphenyl)isoxazol-5-yl]heptanoic acid methyl ester (7.80 g, 55%).